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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/039,171	01/03/2002	Robert Haley	UTSD:749US	7156

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/039,171	HALEY ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9-25 and 36-43* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,9-25,36-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

In view of the Appeal Brief filed on 7/21/08, PROSECUTION IS HEREBY REOPENED. The indicated allowability of claims 17 and 18 is withdrawn upon further consideration of the totality of the prior art reference(s) of record. New rejection set forth below.

To avoid abandonment of the application, appellant must exercise one of the following two options:

(1) file a reply under 37 CFR 1.111 (if this Office action is non-final) or a reply under 37 CFR 1.113 (if this Office action is final); or,

(2) initiate a new appeal by filing a notice of appeal under 37 CFR 41.31 followed by an appeal brief under 37 CFR 41.37. The previously paid notice of appeal fee and appeal brief fee can be applied to the new appeal. If, however, the appeal fees set forth in 37 CFR 41.20 have been increased since they were previously paid, then appellant must pay the difference between the increased fees and the amount previously paid.

A Supervisory Patent Examiner (SPE) has approved of reopening prosecution by signing below:

/JD Schultz, PhD/

Supervisory Patent Examiner, Art Unit 1635

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-5, 10-13, 17-25, 37-39 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radtke (US 6,521,226) taken with Li et al. (C39) and Davies et al. (C14), Adkins (C2), and Humbert et al. (C26). Radtke teaches that paraoxonase-1 (PON-1), when expressed has hydrolase activity for organophosphate. See columns 1 and 15-16. Radtke teaches that PON1 type R and Q are known variants in humans

(columns 4-5 and 15-16). Radtke teaches using PON 1 in gene therapy using a number of viral vectors comprising and methods of delivery are known in the prior art (column 8-9). PON1 type Q phenotype has been correlated with higher paraoxonase activity than the type R phenotype (column 8). Radtke teaches using several routes of administration (including intravenous) to deliver the composition to a subject (column 6). An assay can be used to measure either phenotype or the ratio of the two phenotypes present in an individual (column 8). However, Radtke does not specifically teach identifying a subject at risk or exposed to an organophosphate toxin and administering an expression cassette comprising a nucleic acid encoding PON1 to the subject.

However, at the time the invention was made, Li et al. teach that paraoxonase protects animals against an organophosphate toxin (page 219). Li further teaches identifying animals that have been exposed to an organophosphate toxin (pages 220-221). Li teaches intravenous (i.v.) administration of PON to a mouse exposed to an organophosphate toxin (page 221).

In addition, at the time the invention was made, for three decades it has been established that the main determinant of susceptibility to organophosphate poisoning is the activity level of PON 1 isoenzymes, and this relationship has been shown to hold across many species including humans. Davies teaches, "interspecies differences in PON1 activity correlate well with observed median lethal dose (LD_{50}) values [of organophophates]." See abstract. Adkins and Humbert teach that PON1 type R hydrolyzes paraoxon rapidly (page 598 and page 73, respectively). Davies teaches that PON1 type Q efficiently hydrolyzes diazoxon, soman and sarin (page 334).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to identify an animal exposed to an organophosphate toxin and express PON 1 in a cell or subject exposed to the organophosphate toxin. One of ordinary skill in the art would have been motivated to combine the teaching to protect a cell or subject from an organophosphate toxin. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to intravenously administer a nucleic acid encoding PON1 type R to a subject exposed to paraoxon. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to cells for expressing of PON1 type R and PON1 type R is known to rapidly hydrolyze paraoxon. See ***KSR v. Teleflex***.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to intravenously administer a nucleic acid encoding PON1 to a subject exposed to sarin. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to

cells for expressing of PON1 type Q and PON 1 type Q is known to efficiently hydrolyze sarin. See ***KSR v. Teleflex***.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke taken with Li, Adkins, Humbert, and Davies, namely to intravenously administer a nucleic acid encoding PON1 to a subject exposed to an organophosphate toxin. One of ordinary skill in the art would have been motivated to combine the teaching to sufficiently deliver the nucleic acid to cells for expressing of PON1. See ***KSR v. Teleflex***.

In addition, the method in claims 17 and 18 are obvious because the method taught by Radtke, Li, Adkins, Humbert, and Davies uses the same material and method steps as recited in claims 17 and 18. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/21/08 have been fully considered but they are not persuasive.

In response to applicant's argument that there is no evidence of record to support that one of ordinary skill in the art would expect the teaching in the combination of

references would reasonable result in success in practicing the claimed invention, the argument is not found persuasive because the PON1 type R and PON1 type Q were known, at the time the invention was made, to hydrolyze organophosphate toxins. See Humber, Adkins, and Davies, all of record. Also see Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007).

In addition, at the time the invention was made, there was a reasonable expectation of success of using nucleic acid delivery to efficiently express a protein of interest in cells in vivo (See Radke, of record). "The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success." See Agrizap, Inc. v. Woodstream Corp., 520 F.3d 1337 (Fed. Cir., 2008) and In re Merck & Co., Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Also see Ex parte Kubin, 83 USPQ2d 1410 (Bd. Pat. App. & Int. 2007). "when there is motivation to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense."

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). This is the case here. The totality of the prior art would lead one of ordinary skill

in the to art to practicing the claimed invention with a reasonable expectation of success. See In re Merck & Co., Inc., Id.

In response to applicant's argument that applicant find it nothing short of shocking that the USPTO is taking the position that gene therapy is not an unpredictable art and that it is not necessary to discuss the general position of the PTO on gene therapy here for the simple reasons that the examiner has already gone on the record that gene therapy is unpredictable and the examiner cannot now argue that there is only attorney argument to support this issue, the argument is not found persuasive because as set forth in previous office actions, applicant's argument successfully rebutted the prima facie enablement rejection. Thus, the enablement rejection is withdrawn based on applicant's arguments. See MPEP 2164.05. With respect to applicant's comments directed to a general position of the USPTO on gene therapy, applicant is directed 37 CFR 1.3 Business to be conducted with decorum and courtesy to when commenting on practices of the USPTO.

In response to applicant's argument that there is clearly no "finite number of identified, predictable solutions" from which the skilled artisan could choose based on prior art that gave either no indication of which parameters were critical or no direction to which any possible choices are likely to be successful (See In re O'Farrell and KSR International Co.), the argument is not found persuasive because, at the time the invention was made, PON 1 enzymes, including PON 1 type Q and PON 1 type R were known to one ordinary skill in the art for hydrolyzing organophosphate toxins. See Adkins, Humbert, Davies, and Radtke. In addition, expression a protein in cells in vivo

using nucleic acid delivery was well known to one of ordinary skill in the art. "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Claims 1, 9, 14-16, 21, 36, and 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Radtke taken with Li, Davies, Adkins, and Humbert as applied to claims 1-5, 10-13, 17-25, 37-39 and 43 above, and further in view of Scheffler (US 5,721,118).

However, Radtke taken with Li, Adkins, Humbert, and Davies taken with do not specifically teach using a polyadenylation (poly A) tail in the vector.

However, at the time the invention was made, one of ordinary skill in the art understands that poly A tail protects mRNA molecule from exonucleases and is important for transcription termination, for export of the mRNA from the nucleus and for translation. Scheffler teaches using poly A tail for regulating gene expression (column 5). In addition, tissue-specific, constitutive, and inducible promoters for expressing a gene of interest were well known to one of ordinary skill in the art as exemplified by Scheffler (column 6).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke, Li, Adkins, Humbert, and Davies taken with Scheffler, namely to make and use a poly A tail in the vector in the method. One of ordinary skill in the art would have been motivated to

combine the teaching for protecting the mRNA from exonucleases and for proper polyadenylation of the gene transcript.

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Radtke, Li, Humbert, Adkins, and Davies taken with Scheffler, namely to make and use a promoter selected from a constitutive promoter, an inducible promoter, or a tissue specific promoter in the vector in the method. One of ordinary skill in the art would have been motivated to combine the teaching for properly or efficiently expressing the DNA encoding PON1 in a desired cell.

In view of the teaching of Radtke, Li, Humbert, Adkins, Davies, and Scheffler, one of ordinary skill in the art would have had a reasonable expectation of success for practicing the method because the promoter were well known to one of ordinary skill in the art for expressing a heterologous nucleic acid in a cell.

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 7/21/08 have been fully considered but they are not persuasive for the reasons set forth above in the response to applicant's arguments against first 103(a) rejection and no new arguments are provided for this 103(a) rejection.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-

0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635